Process Validation Considerations

Changing the Paradigm of Process Validation

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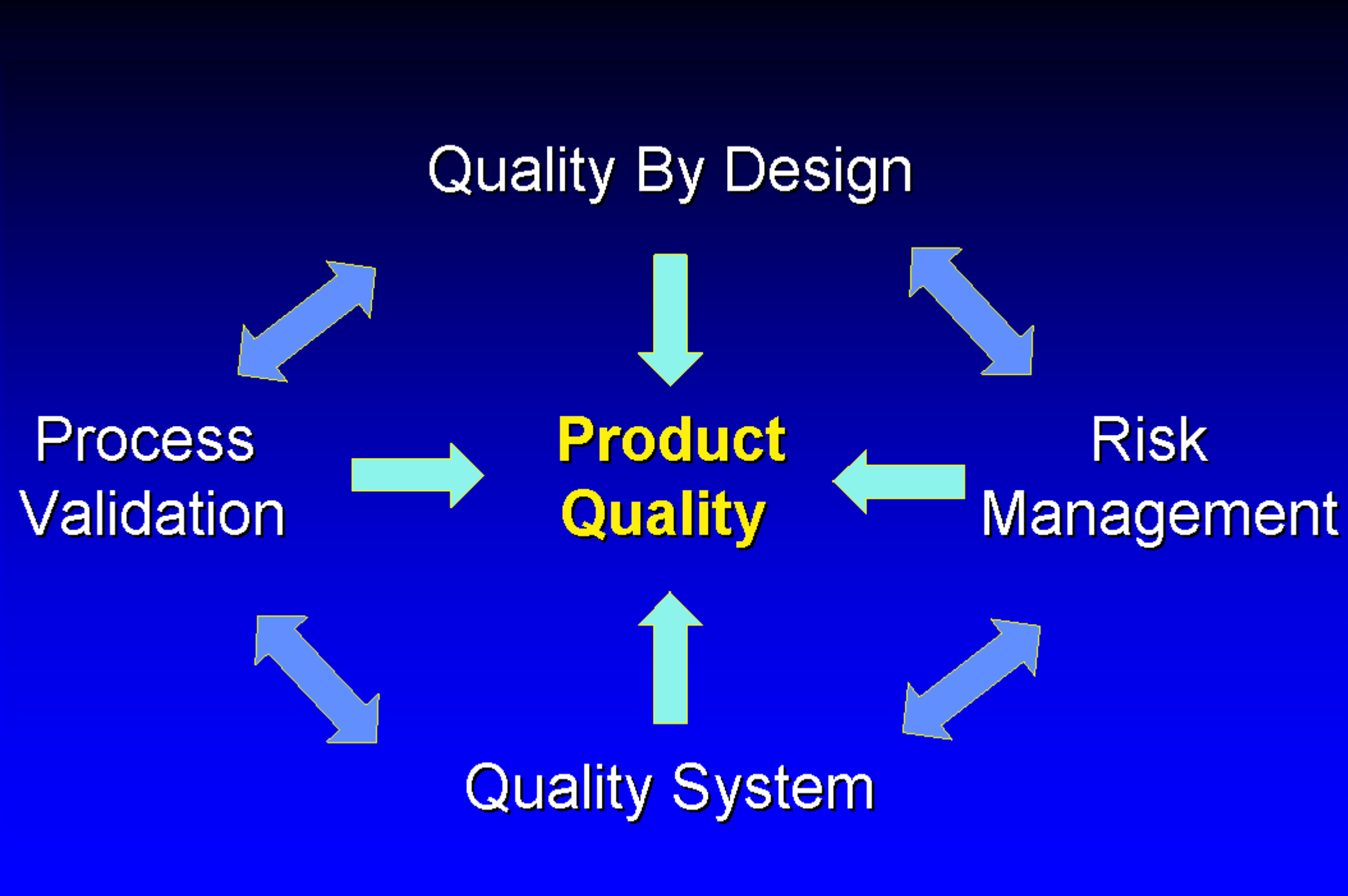
Presentation Overview

- Process Validation
- Principle, Goals, and Considerations
- Lifecycle Approach to Process Validation
- Some Current Issues in Process Validation

So What's New?

Considerations

- CGMP Initiative For the 21st Century
  - Desired State of Manufacturing
  - Facilitate Continuous Improvement and Innovation
  - Process Analytical Technologies
  - Risk Assessment and Mitigation
  - Quality By Design
  - Quality Systems


Quality By Design
Process Validation
Product Quality
Risk Management
Quality System

Reasons For Process Validation

- **Assurance of Product Quality**
  - **Quality safety and effectiveness must be designed and built into the product**
  - **Quality cannot be inspected or tested into the finished product**
  - **Each step must be controlled to maximize the probability that the finished product meets all specifications [**[FDA Guideline General Principles of Process Validation, May 1987]

"Quality By Design"

- **"…quality cannot be tested into product, i.e., quality should be built in by design." [ICH Q8]**
- **" Quality should be built into the product, and testing alone cannot be relied on to ensure product quality" [FDA Quality Systems guidance]**

Validation

- Prospective
- "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics." [FDA Guideline General Principles of Process Validation, May 1987 *emphasis added*]

Principles and Considerations (Goals)

- Demonstrate control of the process
- Demonstrate consistency/ reproducibility of manufacturing a high quality product meeting defined quality attributes
  - Within process operating limits - not to failure
    - "… process when operated according to procedures will consistently yield product with the specified quality attribute."
      [FDA Guideline General Principles of Process Validation, May 1987]

Principles and Considerations (Goals)

- Account for variability – ("Robustness" "Worst Case" "Most Appropriate Challenge")
  - "A set of conditions encompassing upper and lower processing limits and circumstances, including those with the standard operating procedure, which pose the greatest chance of process failure when compared to ideal conditions" [FDA Guideline General Principles of Process Validation, May 1987]
  - **Robustness** - Ability of a process to tolerate variability of materials and changes of process without negative impact on quality – (ICHQ8)

Approaches to PV

- Differing approaches to process validation
  - Empirical approach
    - based upon available information/ manufacturing experience
    - limited design and exploratory studies
  - Is three conformance batches sufficient to demonstrate that a process is validated?
  - How does this approach achieve the goals of validation?

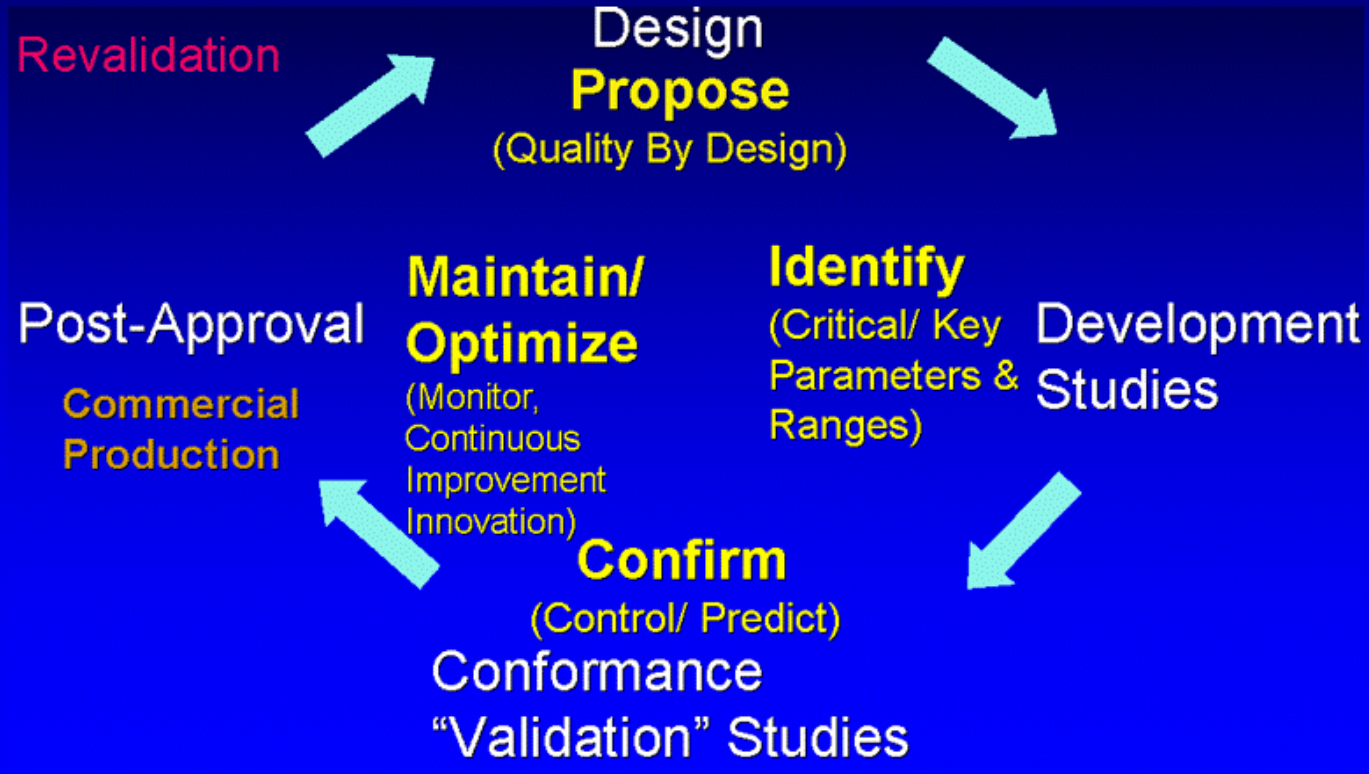
Process Validation - Lifecycle Approach

- Process validation is viewed as a process that occurs throughout the lifecycle of a product
  - **Through a series of activities occurring throughout the product lifecycle, knowledge (collection and evaluation of data) accumulates to support that the process will consistently achieve the intended result (i.e., provide a product meeting predefined attributes) with a high degree of assurance**
- Confidence building activities – increasing assurance
- Point is reached where sufficient knowledge is accumulated to provide assurance to distribute the product
- However, process validation continues and assurance increases throughout the product life-cycle

Process Validation - Lifecycle Approach

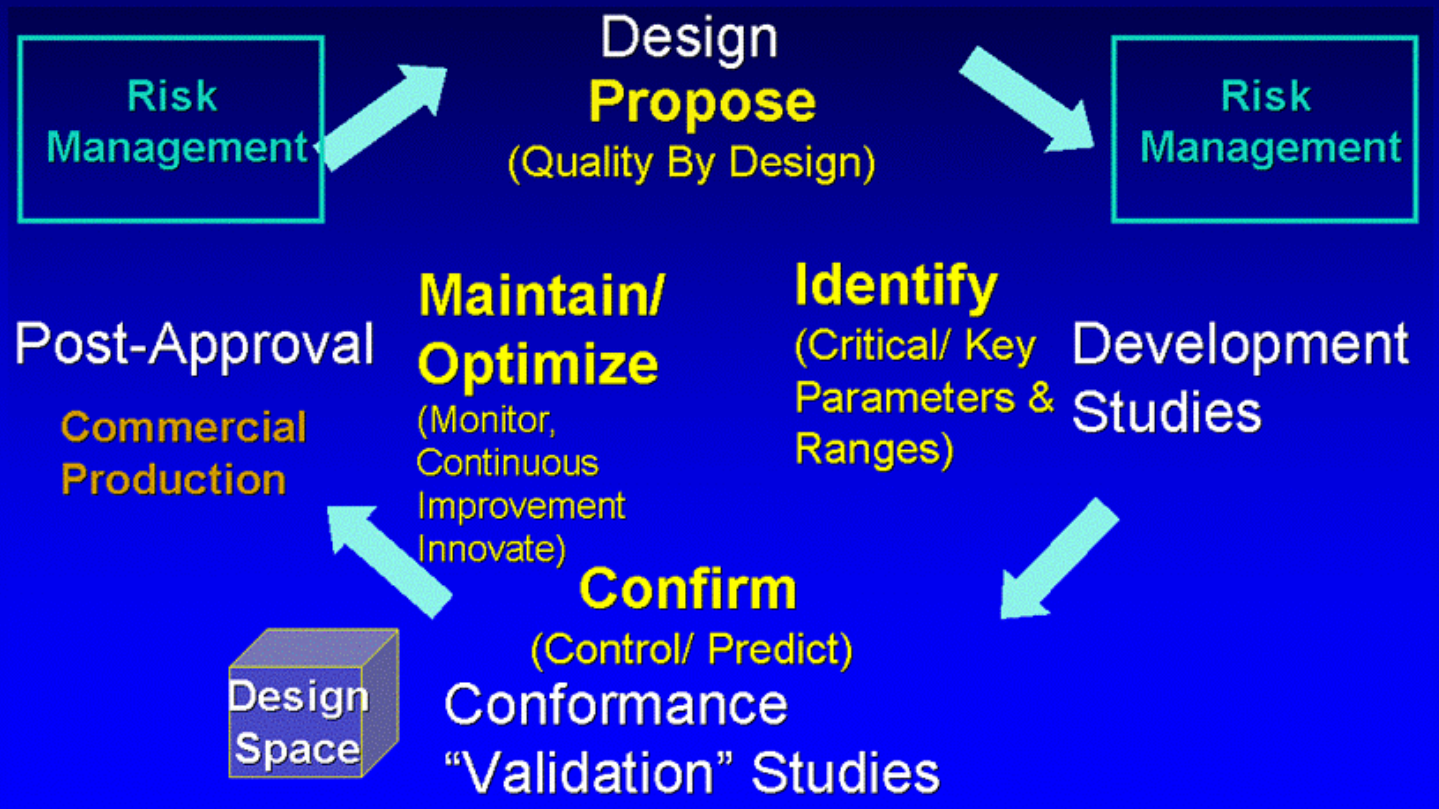
- Reliance on scientific and engineering principles
- Integrated activity requiring expertise and information from multiple areas
- Design Considerations
- Process and product understanding “knowledge”
  - Well defined and designed product and manufacturing process
- Supported by documentation & data starting in development
- Achieve goals of PV
  - Control – Consistency, Variability *(Robustness)*

Validation - Life Cycle Approach
Product Lifecycle



Validation - Life Cycle Approach

Product Lifecycle



Design

- GOAL: Design and evaluate process to propose process steps (unit operations) and process variables (operating parameters) that need to be validated
- Evaluate process by unit operations
- Select process unit operations and process operating parameters to test in “representative” small scale models
  - critical and *questionable* variables
- Justification for selection - Risk Assessment
  - Follows Design Considerations
  - Requires understanding of process and product
  - Based upon experience, knowledge, & understanding,

Development Studies

- GOAL:
  - Identify critical operating parameters & ranges
  - Establish “process robustness” especially multifactor processes
    - Provides assurance of robustness that cannot be achieved at commercial manufacturing scale
    - A ROBUSTNESS STUDY provides assurance that the process will not fail within the defined process control limits
- Understand the process
- Determine process optimum
- Determine capability of a process step (e.g., to remove an impurity, clear a virus)
- Can provides post-approval benefits (e.g., changes, deviations)

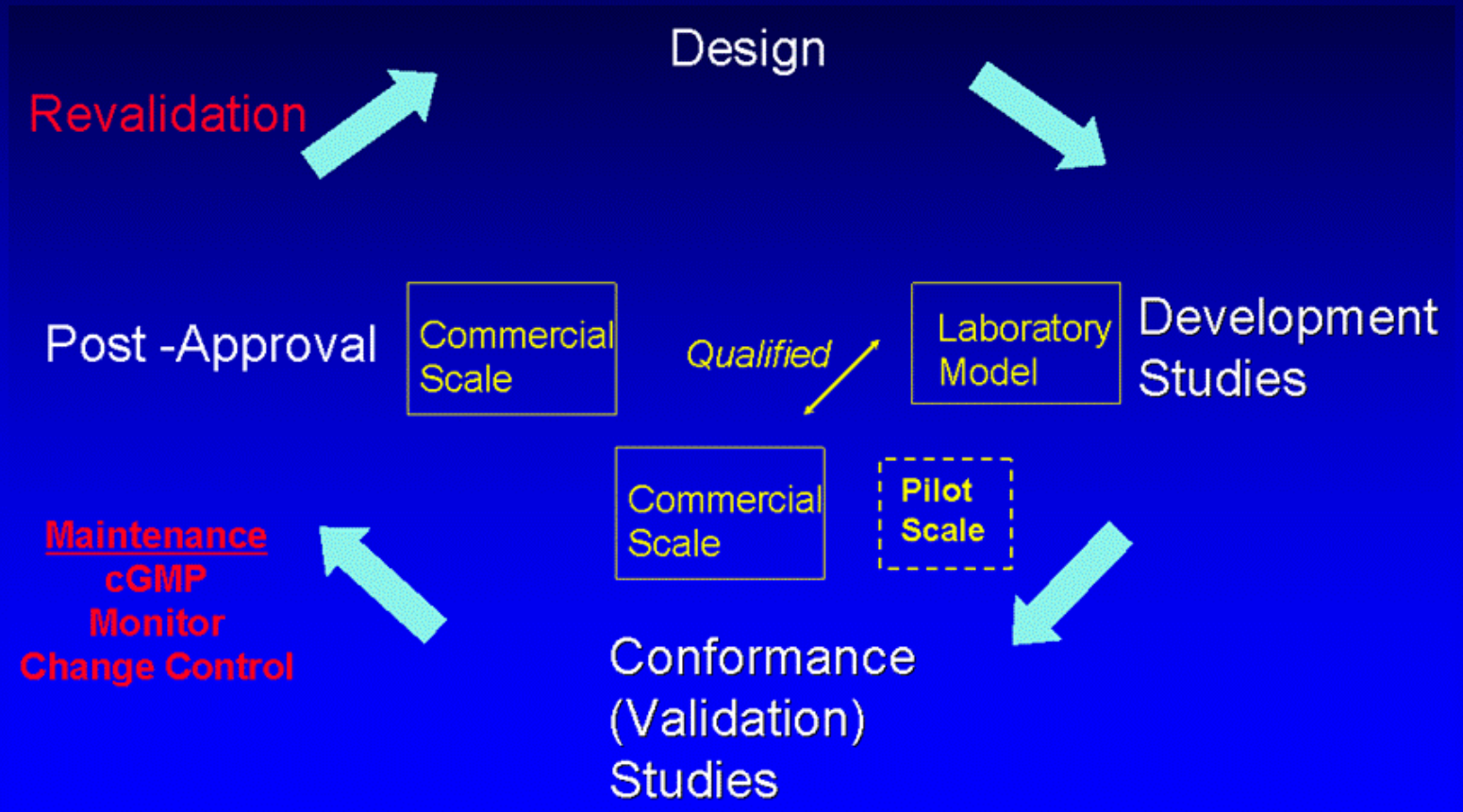
Development Studies

- Scaled-down model (i.e,. laboratory scale) to study and evaluate the process
  - Designed to be representative of the process unit operation and commercial scale (i.e., scale submitted for approval)
- Scientific approximation of the commercial scale manufacturing process
  - Confidence in study and utility of results depends on qualification and conduct of the study
    - How representative of commercial scale are the models?
    - What are appropriate measure of product (intermediate) attributes?
    - Ability to extrapolate models results to commercial manufacture

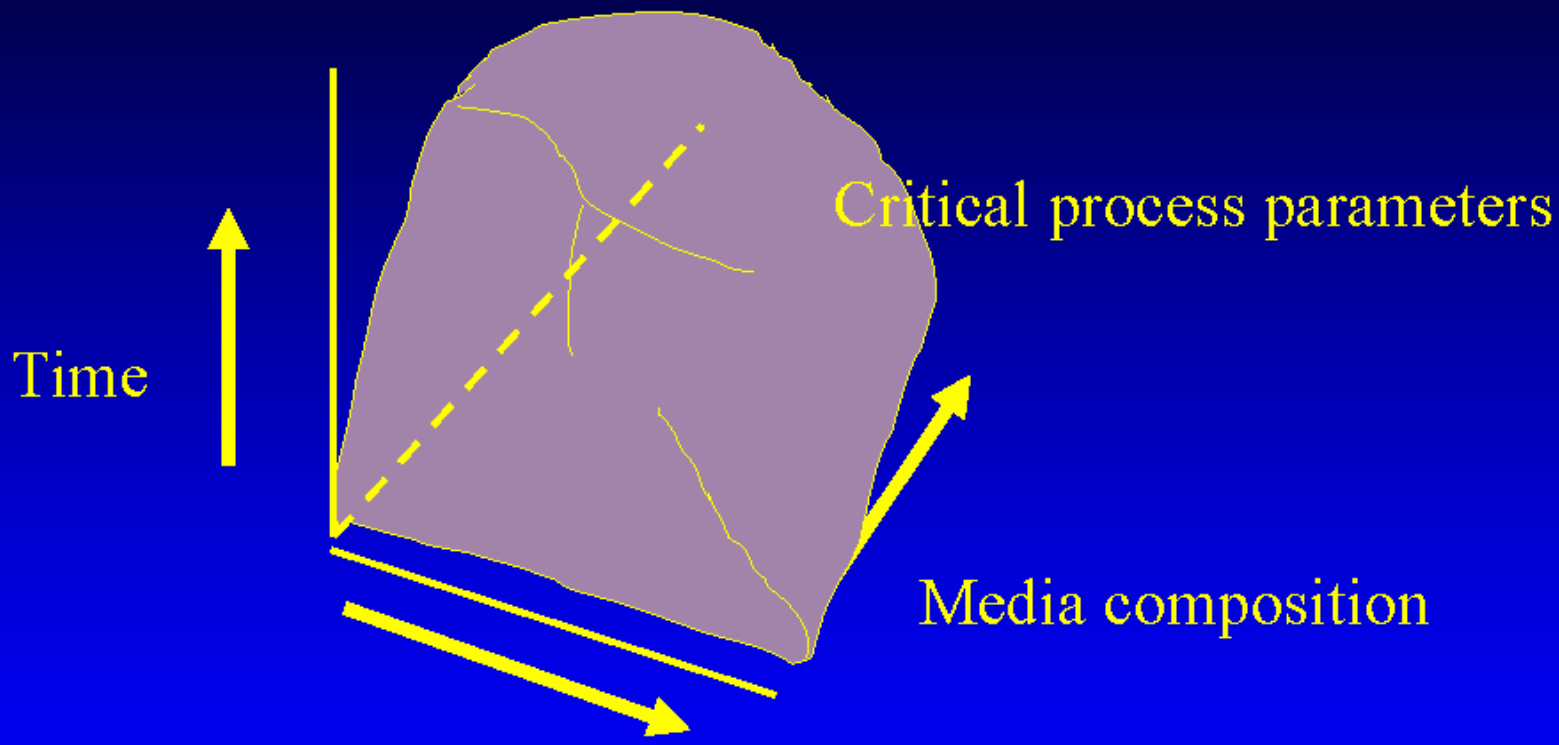
Conformance “Validation” Studies

- **GOAL: Confirm that the commercial process as designed and evaluated can function at commercial scale**
- **Transfer & commercialize information learned in developmental studies**
- **Conformance lots provide some evidence to support the validity and consistency of the process at commercial scale**
- **Follow established Validation Protocol**
  - **Equipment - IQ, OQ, PQ**
  - **Analytical Methods – Qualified/ Validated**
  - **Quality Unit Involvement**
- **Commercial manufacturing scale (i.e., scale submitted for approval)**
  - **Operating parameters are controlled within limits**
    - **Typically operated at target values**
  - **Specified intermediate AND DS/ DP quality is achieved**

Validation - Life Cycle Approach



Design Space (Fermentation)



Equipment ?
Environmental Conditions?

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Commercial Production

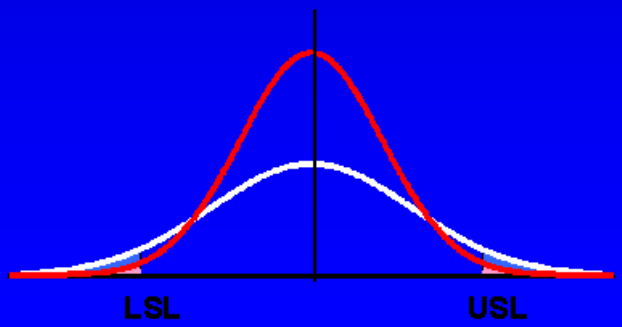
- GOAL: Maintenance of the validated state and implement continual improvement
- Consistent and diligent application of CGMPs
- Effective and robust Quality Unit
- Monitoring and trending of critical operating and performance parameters
  - Statistical Process Control & Other Analysis
  - Corrective and Preventative Action (CAPA)
- Effective change control program
  - Appropriate change control plan and procedures
  - Periodic reassessment of licensed process in light of current knowledge beyond routine change control

Process Capability

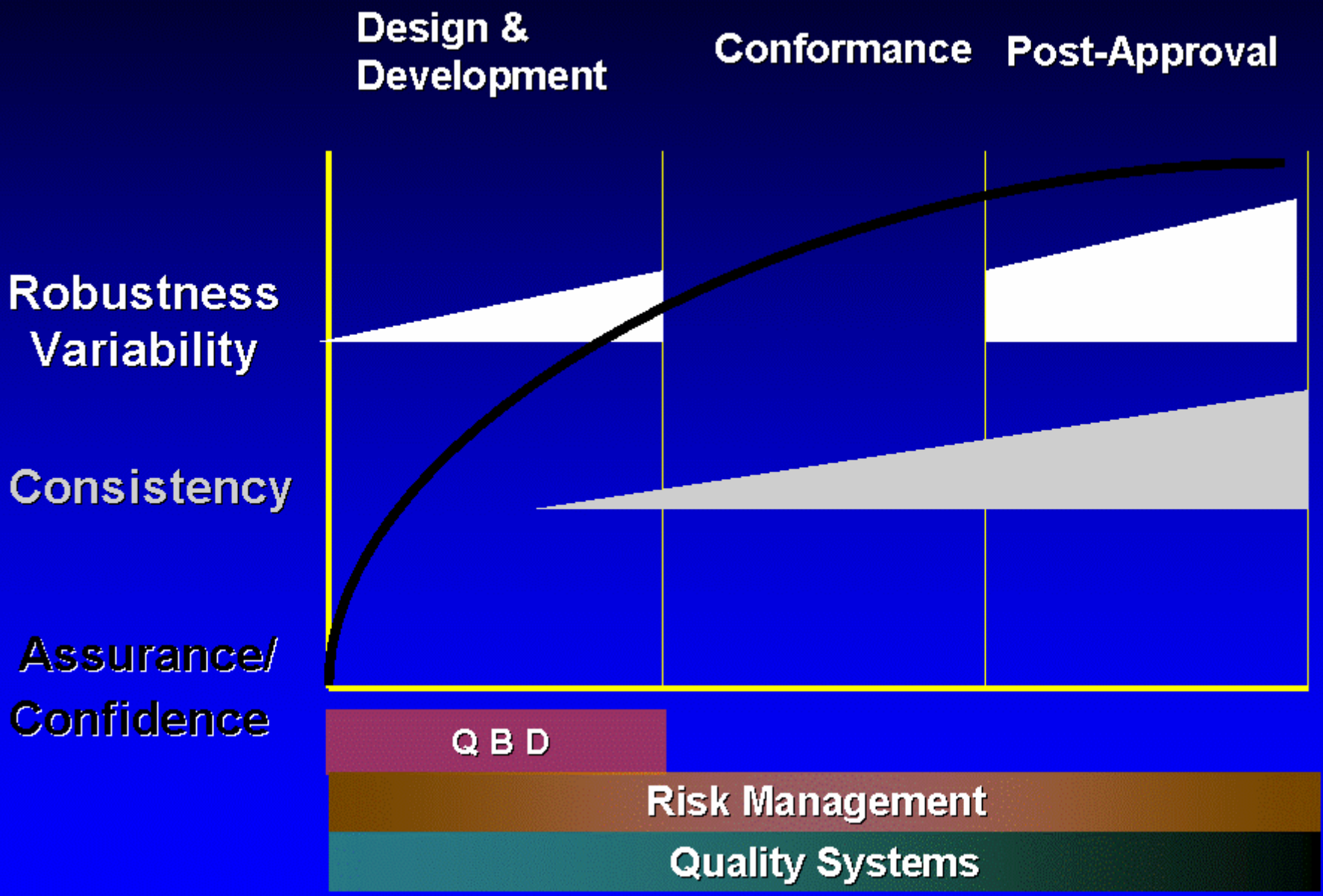
- Process capability (normal manufacturing variation) determined with additional manufacturing
  - Due to variation in components, process, environment, etc.
  - Is a stable and capable process achieved?
    - Estimate and control for critical sources of variability in development?
  - Consideration for Revalidation
- Confidence in achieving desired product quality accumulates with
  - Each lot manufactured especially using new lots of components, at different operating parameter ranges (than target values), different environmental conditions, etc.

Process Capability – Continual Improvement

- With increased knowledge and experience of commercial manufacturing process, process variability should decrease or remain at existing level (as seen in clinical trial experience).
- Risk to quality is reduced by stable and capable manufacturing processes
- Improvement in Quality is a reduction of variability



Lower variability yields lower risk

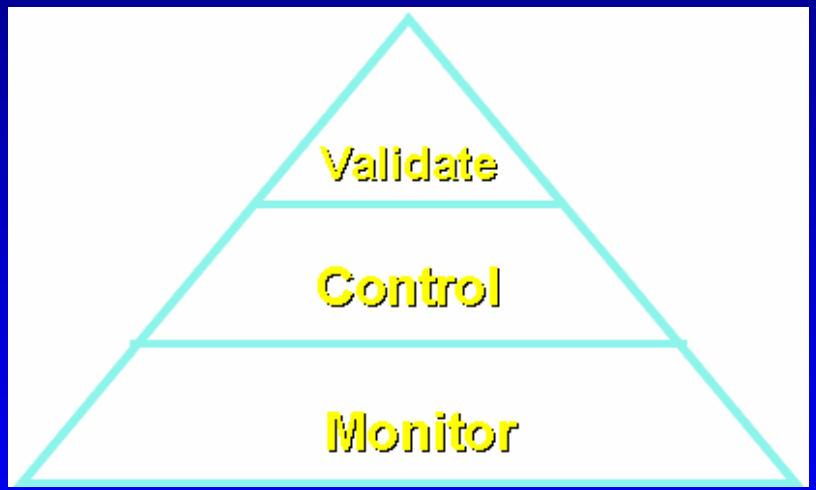

Design &
Development
Conformance
Post-Approval
Robustness
Variability
Consistency
Assurance/
Confidence
Q B D
Risk Management
Quality Systems

Considerations

- Variety of established and developing products
  - Varying complexity
  - Various degrees of process understanding and control
    - Biological and biotechnological products
    - Individualized (customized) therapies
- Ability to measure meaningful quality attributes of Intermediates, Drug Substance, Drug Product?
- To what degree should robustness be demonstrated?
- What is the ability to conduct/ extrapolate small scale studies?
- When is it appropriate to use Generic and Modular validation approaches?
- What impact does modern process control (e.g., PAT) have on validation?

Considerations - What To Validate?

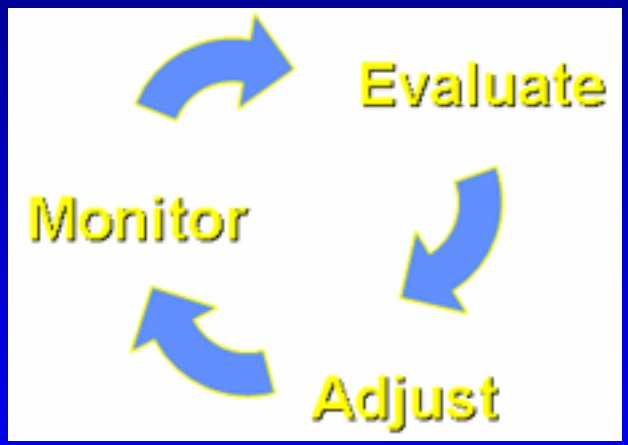
- What do I Validate ?
- What do I Control ?
- What do I Monitor ?



Considerations - What is Critical?

- Critical "A process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification". [ICH Q7A]
- Proposal for Critical & Noncritical Key and Non-key variables
- Important that the manufacturer and regulator knows;
  - **What variables were considered, what variable impacts the process, what variables affect the product (intermediate) quality, or do not (degree & linkage?)**
  - **How variables are controlled, monitored, validated or not, including how suitable acceptance criteria/ limits were determined as applicable**

Considerations “PAT”

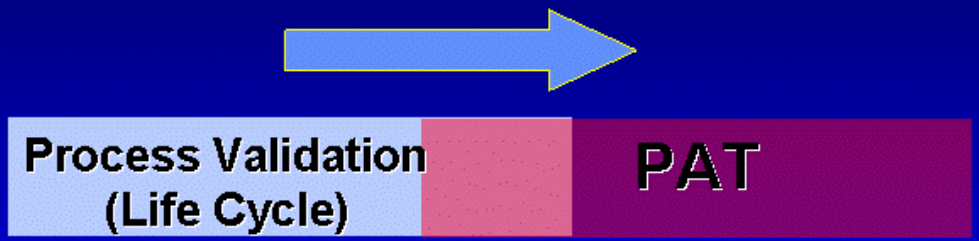


- Control System - Monitoring - Evaluating - Adjusting
  - Continuous “real time” monitoring of product quality attribute (perhaps a surrogate), or process operating parameter
  - Evaluated against data that will allow one to produce an acceptable product or direct evaluation of acceptable product
  - Adjusted (typically automated) to produce an acceptable product
  - System – must be performed in a timely manner (e.g., real-time)

Process Validation and “PAT”

Enhanced Assurance in Product Quality

Increased Manufacturing Efficiency



- **PV (Life cycle - approach) and PAT share elements**
  - **Require process and product knowledge and understanding**
    - **e.g., Design, DOE studies, Statistical Process Control**
  - **Provide an enhanced understanding of the process - continuous process understanding**
  - **Provide a basis for continuous improvements – optimization within existing manufacturing process and equipment that can reduce and accommodate variability**

Process Validation and “PAT”

- Real-time process analysis of quality attributes, can allow for “continuous validation” “continuous verification” of each lot
  - Could potentially reduces reliance on some elements of process validation (e.g., conformance batches)
  - Impact on establishing operating and process parameters & ranges?
  - Impact on establishing the Design Space?

Practical Implications of Process Validation

- Without a comprehensive, lifecycle approach to validate a process, it is more difficult, if not impossible, to:
  - Maintain a State of Control - consistency and control of variability
  - Conduct Technology Transfer
  - Find root cause of nonconformity investigations
  - Implement Change Control
    - Assess potential impact of change,
    - Reduce uncertainties associated with change
  - Execute Continuous Improvement
    - Optimize the process
    - Further reduce variability, improve process capability

So What’s New?

Unanswered questions?

Opportunities?